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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/526,073

02/28/2005

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EXAMINER

RAMIREZ, DELIA M

ART UNIT

PAPER NUMBER

1652

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/526,073	<b>Applicant(s)</b> HOKAZONO ET AL.	
	<b>Examiner</b> Delia M. Ramirez	<b>Art Unit</b> 1652	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 December 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☐ Claim(s) 1 and 6 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 6 is/are allowed.
- 6) ☒ Claim(s) 1 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 28 February 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input checked="" type="checkbox"/> Other: <u>alignment</u> .                        |

## **DETAILED ACTION**

### ***Status of the Application***

Claims 1 and 6 are pending.

Applicant's amendment of claim 1, cancellation of claims 2-5, as well as amendments to the abstract and the title as submitted in a communication filed on 12/5/2007 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### ***Claim Rejections - 35 USC § 112 – Second Paragraph***

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claim 1 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.
3. Claim 1 is indefinite in the recitation of “nucleic acid hybridizing to the nucleotide sequence of SEQ ID NO: 2” for the following reasons. A cursory review of the sequence listing shows that SEQ ID NO: 2 is an amino acid sequence (632 amino acids). In addition, as known in the art, hybridization occurs between nucleic acid molecules. Nucleotide sequences are graphical representations of the order in which nucleotides are arranged in a nucleic acid molecule. Thus, even if SEQ ID NO: 2 were to represent a nucleic acid, a nucleic acid cannot hybridize to a nucleotide sequence. The Examiner attempted to find the nucleotide sequence in the sequence listing that corresponds to a nucleic acid encoding the polypeptide of SEQ ID NO: 1 but none could be found. For examination purposes, it will be assumed that the term reads “nucleic acid that hybridizes to a nucleic acid which encodes the polypeptide of SEQ ID NO: 1”. Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claim 1 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection has been discussed at length in the previous Office action. It is maintained for the reasons of record and those set forth below.

6. The Examiner acknowledges the amendment made to the claim. However, claim 1 as interpreted/amended encompasses a polypeptide which has thermostable ribonuclease H activity and as little as 29% sequence identity to the polypeptide of SEQ ID NO: 1. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. A calculation of the  $T_m$  of a polynucleotide which hybridizes under the conditions recited to a nucleic acid encoding the polypeptide of SEQ ID NO: 1 shows that the recited polynucleotides can be approximately 76.4% sequence identical to a polynucleotide encoding the polypeptide of SEQ ID NO: 2. Using the well known equation of Meinkoth and Wahl (Current Protocols in Molecular Biology, Hybridization Analysis of DNA Blots, pages 2.10.8-2.10.11, 1993),  $T_m = 81.5\text{ }^{\circ}\text{C} + 16.6 \times \log_{10}[\text{Na}^+] + 0.41 \times (\% \text{GC}) - .61 \times (\% \text{form}) - 500/L$ , the corresponding  $T_m$  for the polynucleotide recited is approximately  $73.6\text{ }^{\circ}\text{C}$  assuming a G+C content of 50% and neglecting the term  $500/L$  ( $73.6\text{ }^{\circ}\text{C} = 81.5 + 16.6 \times \log_{10}[3.9 \times 0.1/20] + 0.41 \times (\%50) - .61(\% \text{form} = 0)$ ; for 20xSSC the molar concentration of  $\text{Na}^+$  is 3.9). As known in the art,  $T_m$  is reduced by approximately  $1\text{ }^{\circ}\text{C}$  for each 1% mismatching, therefore under the conditions recited (0.1xSSC and  $50\text{ }^{\circ}\text{C}$ ), a wash at  $50\text{ }^{\circ}\text{C}$  is equivalent to approximately 23.6% mismatching ( $23.6\% = 73.6\text{ }^{\circ}\text{C} - 50\text{ }^{\circ}\text{C}$ ). This level of mismatching amounts to 150 nucleotides which can be modified assuming a coding polynucleotide of 633 nucleotides (SEQ ID NO: 1 has 211 amino acids;  $633 = 211 \times 3$ ;  $150 = 0.236 \times 633$ ). Thus, the genus of polynucleotides recited can potentially encompass

Art Unit: 1652

polynucleotides encoding proteins which are 29% sequence identical to the polypeptide of SEQ ID NO: 1 since the 150 mismatches can potentially alter 150 codons ( $29\% = 100\% - 150 \times 100 / 211$ ). As previously indicated, the specification is silent with regard to the structural features which can be modified in the polypeptide of SEQ ID NO: 1 such that the resulting variant will display the recited enzymatic activity. No correlation between structure and the desired activity has been provided. The specification fails to disclose how to select those variants of the polypeptide of SEQ ID NO: 1 having the recited structural characteristics which have the recited activity. Thus, one cannot reasonably conclude that the entire genus of polypeptides claimed is adequately described by the teachings of the specification.

7. Claim 6 was rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. In view of Applicant's statement in the Remarks section (page 9, first paragraph) indicating that a biological deposit of the recited strain/plasmid was made in accordance with the Budapest Treaty and that the deposit will be available to the public under the conditions specified in 37 CFR 1.108, this rejection is hereby withdrawn.

8. Claim 1 remains rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 1, does not reasonably provide enablement for a structural variant of the polypeptide of SEQ ID NO: 1 which is encoded by a nucleic acid which hybridizes to a nucleic acid encoding the polypeptide of SEQ ID NO: 1 under the conditions recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection is maintained for the reasons of record and those set forth below.

Art Unit: 1652

9. Claim 1 as interpreted/amended encompasses a polypeptide which has thermostable ribonuclease H activity and as little as 29% sequence identity to the polypeptide of SEQ ID NO: 1. See discussion above regarding claim interpretation and scope. Since up to 150 amino acids can be modified and each position can be substituted with up to 19 different amino acids, the total number of variants having the recited structural limitations is immense. The total number of variants of a polypeptide having a specific number of substitutions can be calculated from the formula  $N! \times 19^A / (N-A)! / A!$ , where N is the length in amino acids of the reference polypeptide and A is the number of allowed substitutions. Thus, for a variant of the polypeptide of SEQ ID NO: 1 having 150 amino acid substitutions, the total number of variants to be tested is  $211! \times 19^{150} / (211-150)! / 150!$  (SEQ ID NO: 1 has 211 amino acids) or  $5.0 \times 10^{246}$  variants. Even if it is assumed that the 150 modifications in the nucleic acid result in 50 codon modifications, the number of variants to be tested is still extremely large ( $8.37 \times 10^{113}$  variants). While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that no guidance has been provided regarding the structural features more likely to be associated to the recited enzymatic function such that a limited number of species can be tested, it would require undue experimentation to enable the full scope of the claims. Thus, one cannot reasonably conclude that the claimed genus is fully enabled by the teachings of the specification.

***Claim Rejections - 35 USC § 102***

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Art Unit: 1652

11. Claims 1 and 6 were rejected under 35 U.S.C. 102(b) as being anticipated by Itaya et al. (Nucleic Acids Research 19(16):4443-4449, 1991; cited in the IDS). This rejection has been discussed at length in the Non Final action mailed on 9/5/2007.

12. In view of Applicant's amendment of claims 1 and 6, and the fact that the polypeptide of Itaya et al. appears to be at best 5% sequence identical to the polypeptide of SEQ ID NO: 1 (see attached alignment; 10 matches;  $5\% = 10 \times 100 / 211$ ), this rejection is hereby withdrawn.

13. Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Klenk et al. (PIR accession number E69327, 1997). This rejection has been discussed at length in the Non Final action mailed on 9/5/2007.

14. Applicant argues that the claimed polypeptide is neither taught nor suggested by Klenk et al.

15. Applicant's arguments have been fully considered but are not deemed persuasive. For the reasons extensively discussed above, claim 1 encompasses polypeptides which can be 29% sequence identical to the polypeptide of SEQ ID NO: 1. Since the polypeptide of Klenk et al. is 53% sequence identical to the polypeptide of SEQ ID NO: 1 and the claim does not require the hybridization of the nucleic acid to a specific nucleic acid encoding the polypeptide of SEQ ID NO: 1, the polypeptide of Klenk et al. meets the limitations of the claim as interpreted. Thus, this rejection is maintained.

***Allowable Subject Matter***

16. Claim 6 appears to be allowable over the prior art of record.

Art Unit: 1652

***Conclusion***

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez, Ph.D.  
Primary Patent Examiner  
Art Unit 1652

DR  
February 15, 2008



Art Unit: 1652